Obstetrics and Diagnosis in Freeman-Burian syndrome

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We read with interest the article, "Emergent Cesarean Delivery in a Patient With Freeman-Sheldon Syndrome Complicated by Preeclampsia, Acute Pulmonary Embolism, and Pulmonary Edema: A Case Report," by Drs Fayed, Giska, Shievitz, Attali, and Younger.[1] It is wonderful to see this syndrome discussed. Unfortunately, there were several unclear or inaccurate points, and recent publications were omitted, suggesting an incomplete literature search. As Freeman-Sheldon syndrome, now Freeman-Burian syndrome (FBS),[2] is exquisitely rare, many who believe they have encountered it in clinical practice are eager to publish their experience, despite the perils.

The authors state that, "Patients may have facial abnormalities that put them at risk of difficult airway intubation."[1] This is misleading. Microstomia and whistling face (pursed lips) are required features for an FBS diagnosis and typically make orotracheal intubation difficult, even without additional common but non-diagnostic findings of, "micrognathia, macroglossia, high-arched palate," initially mentioned by the authors.[1,3-5] While some patients with FBS have microglossia—not macroglossia, all patients with FBS are likely to be challenging to intubate.[3-4]

The authors next speak of, "skeletal abnormalities such as joint contractures, scoliosis with resultant restrictive lung disease, and camptodactyly (bent fingers)."[1] In the syndrome, "skeletal malformations" are secondary effects of the primary myopathic process of fibrose tissue replacement of normal muscle fibers.[6] Restrictive plumonary disease results not from abnormal spinal curvatures, which may also include kyphosis or lordosis, but from myopathy of intercostal muscles, often rendering them non-functional.[7] This fibrose tissue acts as constricting bands, the way collagen behaves in severe burns.[6] This is correlated with *in vitro*

molecular myophysiology observations showing problems with the metabolic process for contraction and extreme muscle stiffness that reduces muscular work and power.[6] Misunderstanding of etiology in FBS has led to inappropriate treatment plans, especially surgeries, and has resulted in tragic, lifelong impairments.[3,6-7] Moreover, it is concerning the authors have defined camptodactyly and later talipes equinovarus in a peer-reviewed medical journal where the readership would be expected to understand such terms.

The authors describe inheritance of FBS as being mainly autosomal and X-linked recessive,[1] but it is believed that inherited cases either have a parent with clinical evidence of FBS or rarely are germline mosaicisms[3-4,8]. Most cases, however, are not inherited (sporadic).[3-4] The authors also do not suggest how to diagnose FBS and omit the diagnostic criteria (microstomia, pursed lips, deep nasolabial folds, and H or V-shaped chin defect and two major arthrogryposes—typically, camptodactyly with ulnar deviation and equinovarus).[1,3-4] They specify a few common findings, some of which are included in the diagnostic criteria, but most are not.[1,3-4] Not suggesting a diagnostic pathway, omitting the diagnostic criteria, and listing non-diagnostic findings can confuse the reader unfamiliar with FBS.

The authors also suggest evidence of an association of malignant hyperthermia with FBS and cite a case report of suspected neuroleptic malignant syndrome (NMS) in a patient who purportedly had FBS.[1,9] Some patients with FBS do, indeed, develop hyperpyrexia during general anesthesia, but these hyperpyrexia events, which may include tachycardia and increased muscle rigidity, respond to ibuprofen and also occur where a malignant hyperthermia protocol was followed and in stressful, non-operative stress situations.[4] There is no evidence that MH or NMS is associated with FBS, though FBS anesthesia practice guidelines still suggest following an MH protocol.[5]

In addition to detailing their patient's acute condition and course, the authors only describe their focused pre-anesthesia examination findings and neither specify how their patient met the diagnostic criteria nor provide photographs. As FBS has an estimated false-positive rate of 30-60%,[3] the absence of evidence that the patient met the criteria for FBS raises serious doubt concerning the patient's diagnosis. Without objective evidence for the patient's FBS diagnosis, the purpose for the case report is lost.

The authors emphasize the importance of being aware of the special anesthesia challenges and concerns involved in the care of patients with FBS, which they assert involves, "a difficult airway, underlying restrictive lung disease, and bone fragility."[1] While all patients with FBS can be expected to have a difficult airway,[5] it is unknown how frequent restrictive pulmonary disease may be,[7] and bone fragility is not a finding associated with FBS. Bone strength is reduced following tooth loss and in areas with fibrose tissue restricting or replacing muscle, which may be responsible for the reported fracture rate of 23%[4]. No explanation was given, and less than half of survey participants responded to the question.[4] There is no evidence or suggestion of a primary bone pathology.[3-4]

So far, we have identified ten English-language case reports purportedly describing FBS published between 2020-2022 that contained similar, preventable errors.[1,10-18] Not conducting a thorough literature search and omitting recent articles was the common denominator among the articles.[19] In trying to address the shortcomings of each, we have responded to eight, with four letters already published.[19-22] While problematic in several ways, this article illustrates the potential perils of describing a rare condition.

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